How is the 1,2-Alternate Conformer Formed in Tetra-*O*-alkylation of *p-tert*-Butylcalix[4]arene?

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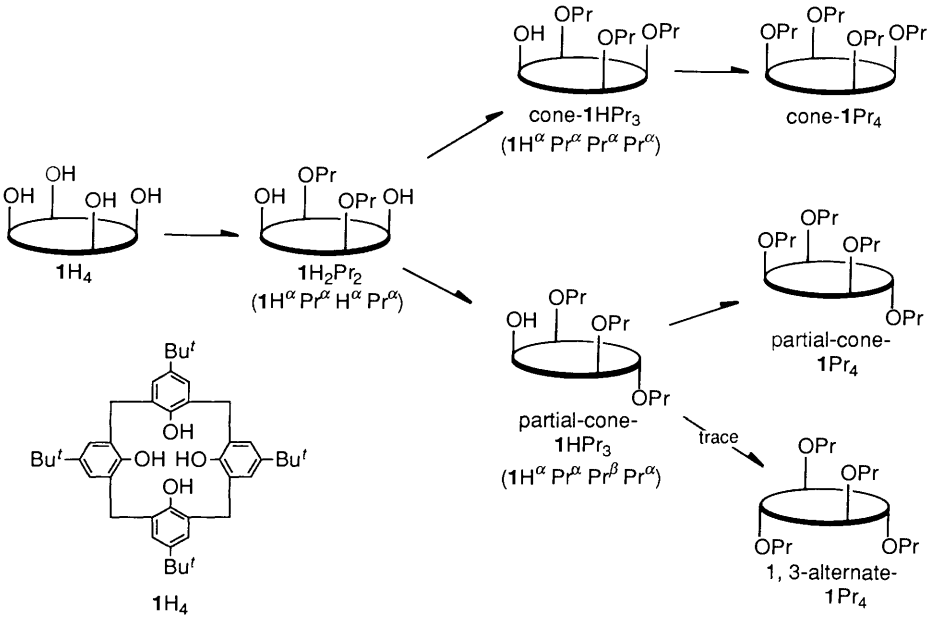
The reaction route for the formation of a new 1,2-alternate conformer from *p-tert*-butylcalix[4]arene has been elucidated.

Calix[4]arenes, cyclic tetramers made up of phenol and formaldehyde, when unmodified adopt a cone conformation as a result of stabilization by intramolecular hydrogen-bonding interactions.[1,2] Introduction of bulky substituents into the OH groups, however, suppresses the oxygen-through-the-annulus rotation and results in conformational isomers;[3,4] the n-propyl group (Pr) is bulky enough to achieve this.[4] Basically, tetra-*O*-alkylcalix[4]arenes can exist as one of four conformers: they are cone, partial cone, 1,2-alternate and 1,3-alternate. *p-tert*-Butylcalix[4]arene ($\mathbf{1H_4}$) when tetra-*O*-propylated with n-propyl bromide (PrBr/NaH, a typical tetra-*O*-alkylation method[3,4]), gave a mixture of cone-$\mathbf{1Pr_4}$ (42%), partial-cone-$\mathbf{1Pr_4}$ (55%) and 1,3-alternate-$\mathbf{1Pr_4}$ (3%), no 1,2-alternate-$\mathbf{1Pr_4}$ being detected (run 1 in Table 1).[4,5] Examination of the reaction route by a stepwise method (*i.e.*, the reaction with PrBr in the presence of NaH was initiated from di-*O*-propylated $\mathbf{1H_2Pr_2}$ or tri-*O*-propylated $\mathbf{1HPr_3}$ and the conformer distribution was examined by HPLC and ^{1}H NMR) established that when NaH is used as base, tetra-*O*-propylation proceeds according to Scheme 1: that is, the conformer distribution is apparently determined when the third propyl group enters (runs 2–4 in Table 1).[6]

We recently found that use of Cs_2CO_3 as base instead of NaH, gave a mixture of partial-cone-$\mathbf{1Pr_4}$ (34%), 1,2-alternate-$\mathbf{1Pr_4}$ (9%) and 1,3-alternate-$\mathbf{1Pr_4}$ (57%), no cone-$\mathbf{1Pr_4}$ being detected (run 5 in Table 1).[7] To the best of our knowledge, this is the first synthesis of a 1,2-alternate conformer by tetra-*O*-alkylation of $\mathbf{1H_4}$. The formation of 1,3-alternate-$\mathbf{1Pr_4}$ as a main product can be explained by facile inversion of the remaining OH group in *O*-propylation of $\mathbf{1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}}$ * in the presence of Cs_2CO_3. This means that the reaction route in Scheme 1 is due to the metal (Na^+) template effect, which is not the case when Cs_2CO_3 is used as base. In contrast, the formation of 1,2-alternate-$\mathbf{1Pr_4}$ cannot be explained on the basis of Scheme 1. In fact, *O*-propylation of $\mathbf{1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\alpha}}$ (a key intermediate in Scheme 1) in DMF in the presence of Cs_2CO_3 yielded partial-cone-$\mathbf{1Pr_4}$ (23%), 1,3-alternate-$\mathbf{1Pr_4}$ (77%) and no 1,2-alternate-$\mathbf{1Pr_4}$ (run 6 in Table 1). How, then, is the 1,2-alternate conformer formed from $\mathbf{1H_4}$?

As a working hypothesis, we assumed $\mathbf{1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}}$ to be a precursor of 1,2-alternate-$\mathbf{1Pr_4}$. We thus synthesized this compound according to Scheme 2. The basic idea of this synethetic method is to use a benzyl group as a protecting group. Compound $\mathbf{1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}}$ (m.p. 120–121 °C) was identified on the basis of IR and NMR spectroscopic evidence and elemental analysis.



Scheme 1 Reaction route for *O*-propylation in the presence of NaH

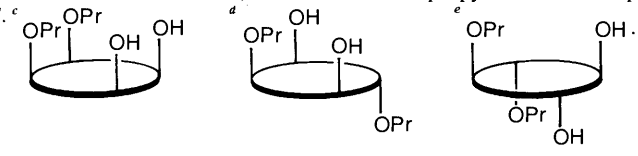
Next, we treated $\mathbf{1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}}$ with PrBr in DMF in the presence of Cs_2CO_3. The product contained partial-cone-$\mathbf{1Pr_4}$ (16%) and 1,2-alternate-$\mathbf{1Pr_4}$ (84%) (run 7 in Table 1). The result established that $\mathbf{1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}}$ is a potential candidate for the precursor of 1,2-alternate-$\mathbf{1Pr_4}$; is this compound then, really contained in the reaction mixture? We followed the

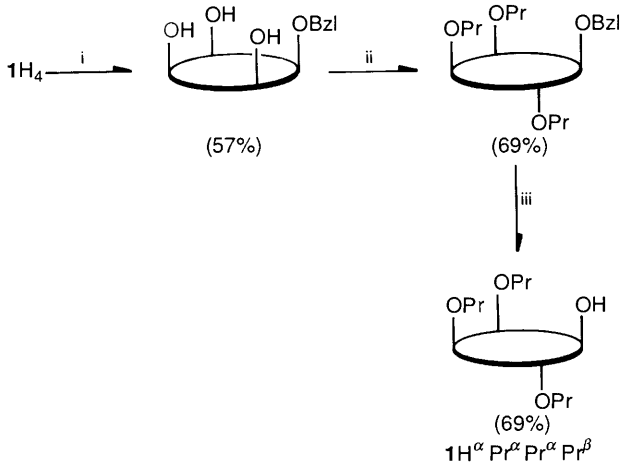
* To distinguish conformational isomers, we used α and β (for example, $\alpha\alpha\alpha\alpha$ for cone and $\alpha\beta\alpha\beta$ for 1,3-alternate) as used in the nomenclature for porphyrin atropisomers.

Table 1 Conformer distribution for *O*-propylation in the presence of NaH[a] or Cs_2CO_3[b]

Run	Starting material	Base	Conformer distribution in $1Pr_4$			
			Cone	Partial cone	Alternate 1,2	Alternate 1,3
1	$1H_4$	NaH	42	55	0	3
2	$1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\alpha}$	NaH	45	52	0	3
3	$1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\alpha}$	NaH	100	0	0	0
4	$1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$	NaH	0	93	0	7
5	$1H_4$	Cs_2CO_3	0	34	9	57
6	$1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\alpha}$	Cs_2CO_3	0	23	0	77
7	$1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$	Cs_2CO_3	0	16	84	0
8	$1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\alpha}$[c]	Cs_2CO_3	0	92	8	0
9	$1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$[d]	Cs_2CO_3	0	15	85	0
10	$1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$[e]	Cs_2CO_3	0	15	11	75

[a] THF–DMF (10:1 v/v), 2 h at the reflux temperature. The *O*-propylation reactions proceeded quantitatively. For further details of the reaction conditions see ref. 7. [b] DMF, 3 h at 70 °C. The *O*-propylation reactions proceeded quantitatively. For further details of the reaction conditions see ref. 7. [c] [d] [e]





Scheme 2 *Reagents:* i, $C_6H_5CH_2Br$/NaH in toluene; ii, PrI/NaH in THF; iii, Me_3SiBr in chloroform

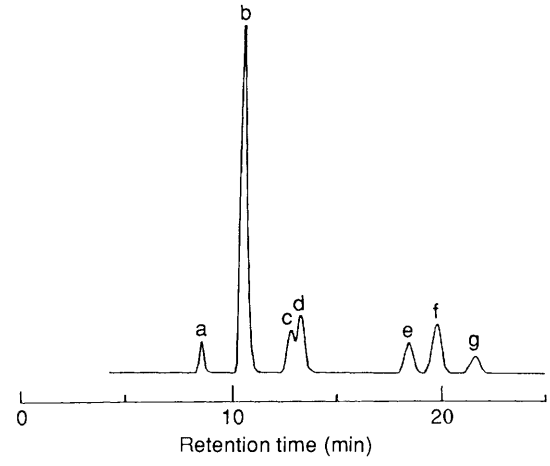


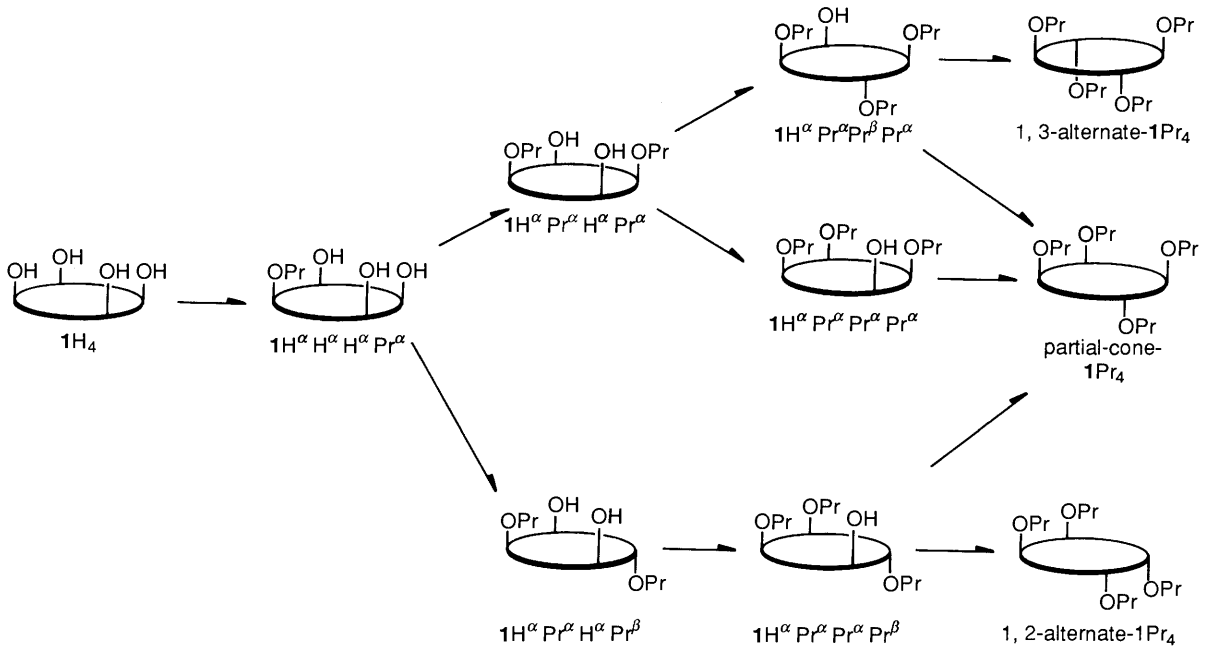
Fig. 1 High-pressure liquid chromatogram for the mixture from the reaction of $1H_4$ and PrBr in DMF in the presence of Cs_2CO_3: mobile phase, chloroform:methanol = 1:5 (v/v); stationary phase Du Pont Zorbax ODS; (a) $1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\alpha}$, (b) $1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$, (c) $1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$, (d) $1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\alpha}$, (e) partial-cone-$1Pr_4$, (f) cone-$1Pr_4$ and (g) 1,2-alternate-$1Pr_4$

reaction of $1H_4$ and PrBr in DMF in the presence of Cs_2CO_3 by an HPLC method (see in Fig. 1). In tetra-*O*-propylation of $1H_4$ we always observed seven peaks. Among them we could assign six peaks to $1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\alpha}$ and conformational isomers of $1HPr_3$ and $1Pr_4$ but could not assign the peak (c) which appeared between $1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$ [peak (b)] and $1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\alpha}$ [peak (d)]. We found that the authentic sample for $1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$, newly synthesized by the present protection–deprotection method, shows the retention time exactly equal to this peak. We isolated this compound by a preparative TLC method and confirmed that the m.p. and the ^1H NMR spectrum are the same as those of $1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$.*

It is now clear that $1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$ is the intermediate to yield 1,2-alternate-$1Pr_4$. The possible precursors of this compound are $1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\alpha}$, $1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$ and $1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$. We synthesized these di-*O*-propylated isomers by using a protection–deprotection method and metal template effects.[8]* The reaction of these compounds with PrBr in the presence of Cs_2CO_3 results in the conformer distribution as shown in Table 1 (runs 8–10). Compound $1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$ gave partial-cone-$1Pr_4$ (15%) and 1,2-alternate-$1Pr_4$ (85%). This conformer distribution is in good accord with that from the reaction of $1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$ and PrBr in the presence of Cs_2CO_3 [run 7 in Table 1: partial-cone-$1Pr_4$ (16%) and 1,2-alternate-$1Pr_4$ (84%)]. In fact, we could detect the peak for $1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$ by HPLC analysis when 1 mol equiv. of $1H_4$ was treated with 2 mol equiv. of PrBr in the presence of Cs_2CO_3. In contrast, the yield of 1,2-alternate-$1Pr_4$ from $1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\alpha}$ and $1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$ was very low (8 and 11%, respectively). On HPLC analysis the peaks for these isomers were not detected.

As a summary of the foregoing findings we can now propose a reaction route for the formation of 1,2-alternate-$1Pr_4$ as in Scheme 3. The low yield (9%) of 1,2-alternate-$1Pr_4$ in tetra-*O*-propylation of $1H_4$ in the presence of Cs_2CO_3 is explained as such that $1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$ is not a major intermediate among $1H_2Pr_2$ isomers.

* We heated conformational isomers of $1H_2Pr_2$ and $1HPr_3$ in THF at the reflux temperature for 24 h. The HPLC analysis of the recovered samples established that isomerization *via* PrO-through-the-annulus rotation does not take place.



Scheme 3 Reaction route for *O*-propylation in the presence of Cs_2CO_3

As described in the introduction, the reaction of $\mathbf{1}H_4$ and PrBr in the presence of NaH yields cone-$\mathbf{1}Pr_4$ and partial-cone-$\mathbf{1}Pr_4$ in addition to a trace amount of 1,3-alternate-$\mathbf{1}Pr_4$ whereas that in the presence of Cs_2CO_3 yields 1,2- and 1,3-alternate-$\mathbf{1}Pr_4$ in addition to partial-cone-$\mathbf{1}Pr_4$. It is known that Na^+ is strongly bound to tetra-*O*-alkylated cone-shaped calix[4]arene whereas Cs^+ is not.[9] We consider, at present, that tetra-*O*-propylation of $\mathbf{1}H_4$ favourably affords the conformational isomers with inversed phenol units (such as 1,2- and 1,3-alternate-$\mathbf{1}Pr_4$) whereas cone-$\mathbf{1}Pr_4$ is formed in significant yield only when metal cations added as base exert the metal template effects.

In conclusion, the present paper elucidates for the first time the route for the formation of 1,2-alternate-$\mathbf{1}Pr_4$ on the basis of stepwise examination of lower *O*-propylated *p-tert*-butylcalix-[4]arenes.

Acknowledgements

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